PATENT

UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 99-849-A)

In the application of:			
Odile Leroy			
Serial No.	**09/423,698**	**Examiner:**	**Duffy, P.A.**
Filed:	**February 10, 2000**	**Group Art Unit:**	**1645**
Title	**Multivalent Vaccine Composition with Mixed Carrier**	**Confirmation No.:**	**7060**

REPLY BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Reply is responsive to the Examiner's Answer mailed on June 2, 2005.

It is believed that no fee is due in connection with this filing; however, if a fee is due the Commissioner is authorized to charge our Deposit Account No. 13-2490.

In the "Grouping of the Claims" paragraph, the Examiner stated that the rejection of claims 1-24 stand or fall together because Appellant's brief does not include a statement that this grouping of claims does not stand or fall together and the reasons in support thereof.

However, Appellant submits that under the revised rules governing Ex Parte Appeals, Appellant is not required to include a "Grouping of the Claims" paragraph in the Appeal Brief. Effective September 13, 2004, 37 CFR §1.192 was deleted and replaced with 37 CFR §41. Under 37 CFR §41.37, which sets forth the requirements of an Appeal Brief, a grouping of the claims is no longer required.

In the "Grounds of Rejection" paragraph, the Examiner summarizes the teachings of Chu et al and EP 0497525 ("EP '525" or "Merck"). However, the Examiner's summary provides only a partial description of the teachings of the Chu et al reference and, in doing so, neglects other significant teachings, thereby distorting the overall teaching of Chu et al. The failure to consider the teachings of Chu et al. as a whole is expressly prohibited by the Federal Circuit which holds that prior art references "must be read as a whole and consideration must be given where the

references diverge and teach away from the claimed invention." *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F,2d 1471 (Fed. Cir. 1986).

These additional teachings in Chu et al. include the following:

(1) Chu et al. teaches that there is no difference between the immunogenic response induced by conjugates containing the HCH protein ("nonsense" carrier) or the TT protein ("useful" carrier) (page 252, right column and tables 2 and 3). Thus, Chu reports that immunogenic response is the same whether the two conjugates are both coupled to the same carrier protein or to different carrier proteins. This is evidenced, for example, in Table 2 which shows that the response for Hib-HCH + K100-HCH is the same as the response for Hib-HCH + K100-TT. Likewise, the response for Hib-HCH + Pn6A-HCH is the same as the response for Hib-HCH + Pn6A-TT. Based on this teaching, one skilled in the art would conclude, as Chu et al does, that it doesn't matter whether the conjugated carrier proteins are the same or different.

(2) Chu et al. also teaches that when Hib-HCH conjugate is injected with either K100-HCH or K100-TT, the anti-Hib responses were NOT increased over those induced by either conjugate alone (page 253, left column and Table 2). Given that Chu et al. teaches one combination of conjugates that elicits an increased immunogenic response and one combination of conjugates that does not, the teaching of Chu et al as a whole is actually inconclusive as to the whether the use of two conjugates in combination would elicit an increased immunogenic response.

(3) Chu et al. postulates that one explanation for the increased immunogenic response observed with the combination of Hib-HCH conjugate and Pn6A-HCH or Pn6A-TT conjugate is due to the fact that the total amount of the combined polysaccharides was twice the amount of that used with either conjugate alone (page 253, left column). Chu et al further suggests that the lack of response observed with the combined Hib-HCH and K100-HCH or K100-TT conjugates could be due to the fact that the total amount of polysaccharide used in the combined conjugates was the same as the amount administered with the monovalent preparations (page 253, left column). Alternatively, Chu et al explains that the enhanced response elicited by the simultaneous administration of Hib-HCH and Pn6A-HCH or Pn6A-TT conjugates could be due to the cross-immunogenicity between the Hib and Pn6A polysaccharides reported in hyperimmune animal sera (page 253, left column). Thus, while Chu et al. clearly suggests the importance of the polysaccharides for enhancing the immunogenic response observed in

combinations of conjugates, it fails to even contemplate a possible role of the carrier protein in the immunogenic response.

Accordingly, based on the totality of the teachings in Chu et al, namely that (1) not all combinations of multiple (i.e., two) polysaccharide-protein conjugates elicit an increased immunogenic response, (2) the immunogenic response is the same whether the two conjugates are coupled to the same protein or to different proteins, and (3) the observed immunogenic response may be related to characteristics of the polysaccharide, one skilled in the art would not have been motivated by Chu et al to make a composition of polysaccharide conjugates comprising at least two carrier proteins that are different.

Nor is this motivation found in the Merck application. EP '525 teaches compositions comprising a mixture of different *pneumococcal* polysaccharide-carrier protein conjugates (Pn-Ps-PRO) that induce a broadly protective recipient immune response. EP '525 also teaches that immunogenicity can be further enhanced by conjugating the multiple polysaccharides to an immunogenic protein, such as DT or TT. However, EP '525 does not teach the use of two or more different protein carriers in a single conjugate composition. Given that EP '525 reports successful conjugates with enhanced immunogenicity comprising multiple *pneumococcal* polysaccharides conjugated to a single immunogenic carrier protein, there is simply no motivation in EP '525 to seek further *pneumococcal* compositions, much less ones having two or more different protein carriers.

In the "Response to Argument" paragraph, the Examiner addresses arguments set forth in the Appeal Brief. Appellant provides the following answers to Examiner's comments.

First, the Appellant agrees with the Examiner that there is no absolute requirement that the modification, substitution or combination be expressly articulated by the art; however, the motivation to combine the references or the suggestion to make the claimed combination still must be found in the prior art. Appellant submits that there was simply no motivation to combine a reference teaching successful *pneumococcal* conjugates comprising multiple polysaccharides conjugated to a single immunogenic carrier protein with a reference teaching that the immunogenic response is the same regardless of whether two polysaccharide conjugates are coupled to the same protein or to different proteins, to achieve the presently claimed

compositions of *S. pneumoniae* polysaccharide conjugates comprising at least two carrier proteins that are different.

On page 8 of the Examiner's Answer, the Examiner states that "Appellant argue that Chu et al fails to teach the second element, two different carrier proteins" and continues to provide reasons why Appellant's statement is untrue. However, the Examiner has misstated Appellant's argument. Appellant wishes to clarify that it actually stated that "Chu fails to teach the second element (polysaccaride derived from Streptococcus pneumoniae), and while Chu teaches a composition comprising two carrier proteins, Chu fails to provide any teachings suggesting or motivating the use of two carrier proteins generally". (Appeal Brief, page 3).

The Examiner argues on page 9 that the motivation to add the compositions of Chu with the compositions of EP '525 "was expressly provided by EP '525 ... because Merck and Co Inc. teach that vaccines comprising a mixture from one to ten different pneumococcal polysaccharide-immunogenic protein conjugates (Pn-Ps-PRO) induce broadly protective recipient immune responses against cognate pathogens." However, this teaching is merely an example of the use of multiple polysaccharides in the composition and provides no teaching or suggestion whatsoever relating to the carrier protein. The Examiner further states that EP '525 articulates a suggestion that teaches the desirability or advantages of using different carrier proteins (Examiner's Answer, page 9) but fails to point out where such teaching is found in EP '525. Appellant assumes the Examiner refers to the teaching in EP '525 that the protein portion of the conjugate may be an immune enhancer such as diphtheria or tetanus toxoid (Examiner's Answer, page 6 and 9). However, Appellant submits that with respect to the carrier protein, Merck's teaching is limited to the use of a single immunogenic carrier protein. Nowhere in the EP '525 application does Merck teach or suggest the use of at least two different carrier proteins.

The Examiner argues that while obviousness can not be established by combining references without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done, there is no requirement that the prior art provide the same reason as the Appellant to make the claimed invention. (Examiner's Answer, page 10). The Examiner argues that Merck teaches the desirability of combining multiple polysaccharides and also teaches the desirability of conjugating the polysaccharides to an immunogenic protein. The Examiner concludes that "[t]he skilled artisan in this art would

have immediately combined the pneumococcal conjugate compositions." (Examiner's Answer, page 10)

Appellant agrees with the Examiner's statement of law but submits that the Examiner has not provided evidence of the motivating force found in Chu et al or Merck that would compel one skilled in the art to make the claimed polysaccharide compositions comprising at least two different carrier proteins. Merck merely teaches the desirability of using a single immunogenic protein and provides no teaching whatsoever of the desirability of using two or more different immunogenic proteins. For the reasons stated herein and previously, Chu et al also fails to teach the desirability of using two or more different immunogenic proteins.

The Examiner disagrees with Appellant's argument that Chu et al would in fact discourage one from making additional compositions, arguing that while a stronger immunogenic effect using two Hib conjugates over the monovalent Hib preparation was not observed after the third injection, it was observed after the second injection. This argument is a misstatement of Chu's teaching. Chu et al clearly teaches that "[s]imultaneous injection of the K100 and the Hib conjugates did not enhance the anti-Hib response" and "[n]o advantage upon anti-Hib antibody formation was achieved using the K100 conjugates alone or in combination with Hib-HCH." (Abstract and page 253, left column, respectively). Appellant maintains that based on Chu's teaching, one skilled in the art would not have been motivated to use conjugates having two different carrier proteins.

The Examiner also argues that "there is no requirement under 35 USC 103, that the combination provide for an improvement" and further argues that the negative results do not constitute a "teaching away" because some of the compositions (Hib and Pn6A conjugates) did produce the desired antibodies. (Examiner's Answer, page 11). Appellant is not arguing that the claimed combination must effect an improvement, but simply maintaining that the negative results described in Chu et al would discourage, rather than motivate, one skilled in the art to pursue the claimed compositions comprising conjugates having at least two different carrier proteins.

According to the Examiner, Chu et al. teaches the benefits of using a combination of different carriers by reporting the positive results achieved using the Hib and Pn6A conjugates. (Examiner's Answer, page 11). However, the same results are achieved with the simultaneous

administration of Hib and Pn6A conjugates regardless of whether the carrier proteins are the same (both HCH) or different (HCH and TT) (Tables 2 and 3). Thus, it is not clear whether the results are due to the use of two different antigens or two different carrier proteins in the compositions. Moreover, if the results are due to there being two different carrier proteins, they contradict the results where the Hib-HCH/Hib-TT combination was compared directly to Hib-HCH or Hib-TT alone (i.e., no change in immunogenicity). Finally, Chu et al. even fails to attribute the results to the use of two different carrier proteins and instead suggests that the success of the compositions is due to the polysaccharide components. Such contradictory evidence, in the absence of any recognition whatsoever of the possible benefit of using two different carrier proteins, simply does not rise to the level of suggesting the use of two carrier proteins in the polysaccharide compositions.

Appellant disagrees with the Examiner's statement that it is irrelevant whether the results are due to two different antigens or two different carrier proteins because the scientific basis does not have to be articulated (Examiner's Answer, page 13). The underlying scientific basis for an observation is something that could provide a motivation to make the claimed compositions. Where the underlying scientific rationale for a particular result is uncertain, a motivation to make the claimed compositions is also lacking. The uncertain scientific basis in conjunction with the inconsistent results is highly relevant to the determination of whether Chu suggests the use of two carrier proteins in the polysaccharide compositions.

Later on, the Examiner admits that Chu et al establishes that the use of two different carrier proteins in compositions using the same polysaccharide does not improve immunogenicity (Examiner's Answer, page 16), however, the Examiner fails to recognize that such teaching provides no motivation to make a composition comprising two different carrier proteins.

Appellant also disagrees with the Examiner that Appellant is not arguing the references as combined (Examiner's Answer, pages 12 and 14). The Examiner states that "Appellant persists in arguing the references individually, rather than the references combined. The references as combined teach compositions comprising (Hib-carrier and Pn6A-TT form Chu et al) combined with the PRO-PS-Pn of EP '525 ...clearly renders the obvious the instantly claimed invention. As such, the combination is *prima facie* obvious." (Examiner's Answer, page 14).

Appellant submits that this reasoning does not comport with the standards of 35 USC 103. The Examiner is simply assuming the combination of the compositions in the prior art references to argue that the claimed composition is obvious based on the combined compositions. In so doing, the Examiner is engaging in impermissible hindsight, which is prohibited by the Federal Circuit ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" *In re Fritch*, 972 F.2d 1260, 1266, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992) (citations omitted) (quoting *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988)).

Further, in contrast to the Examiners assertion, Appellant is not arguing the references individually, rather Appellant is arguing that there is no motivation to combine teachings of the references by pointing to the deficiencies found in both prior art references and the absence of other prior art teaching compensating for these deficiencies.

The Examiner repeatedly states that the Appellant "misses the point of the rejection, the combination of the Pn6A-carrier conjugate compositions of Chu et al with that of EP '525". (Examiner's Answer, page 13). Appellant fully understands the point of the rejection, but maintains that, based on a reference that provides unclear, inconsistent, and contradictory results with respect to the use of different carrier proteins in polysaccharide compositions in combination with a reference that clearly provides highly successful pneumococcal polysaccharide compositions using only one carrier protein, one skilled in the art would not have been motivated to combine the teachings to make pneumococcal polysaccharide compositions comprising at least two different carrier proteins.

The Examiner states the Appellant's argument that one would hesitate to combine carrier protein antigens for fear of an adverse result unless there is a reasonable expectation of achieving a beneficial result is "ludicrous" and goes on to argue that EP '525 teaches the use of multiple antigens in the combination of multiple pneumococcal polysaccharides for vaccine (Examiner's Answer, page 15). But the Examiner appears to misunderstands the Appellant's point. The Appellants are quite aware that vaccine compositions comprising multiple antigens are

widespread. What the Appellants submit, however, is that those skilled in the art would prefer to avoid using more antigenic substances in a vaccine composition than necessary. And given that the cited art teaches useful compositions, the tendency of those skilled in the art to minimize the number of antigens would be a factor dissuading the introduction of a second carrier protein (another antigenic substance) into an already useful composition absent an unambiguous advantage in doing so (which the Appellants submit is lacking in the cited art).

The Examiner also states that EP '525 teaches the advantages of a polysaccharide-protein conjugate in vaccines for the elderly and infants. However, the teaching in EP '525 is limited to teaching the advantages of multiple antigenic polysaccharides conjugated with a single carrier protein. Neither Chu et al, not EP '525 teach the advantage of using multiple antigenic carrier proteins. In fact, Chu et al cautions against using multiple antigenic carriers and warns that certain types of carrier proteins should be avoided, such as nonsense carrier proteins, to avoid injection of adventitious antigens into infants. (Chu et al, page 252).

The Examiner concludes by making blanket statements about what was known in the art and therefore *prima facie* obvious, further arguing that if the individual components are *prima facie* obvious, the combination of the components was also *prima facie* obvious. Specifically, The Examiner states that "the use of the same or different carriers is *prima facie* obvious. The use of same *pneumococcal* polysaccharides with different carriers is *prima facie* obvious. All *pneumococcal* polysaccharides were known in the art and all carrier proteins were known in the art... The combination of any of the conjugates taught by the prior art in any desired combination is *prima facie* obvious." The Examiner concludes by stating that the claimed invention is drawn to a mere combination of that which was already known in the art and based on the teachings in Chu et al., it was *prima facie* obvious to combine known conjugates in the art. (Examiner's Answer, pages 16-19).

For all of the reasons stated herein and previously in the Appeal Brief and Response to Office Action, Appellant disagrees that it would have been obvious to combine the *pneumococcal* polysaccharides in EP '525 with the conjugates described in Chu et al to arrive at the presently claimed compositions of *pneumococcal* polysaccharide conjugates comprising at least two carrier proteins that are different.

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: August 2, 2005

Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002